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Cerebral Venous Sinus Thrombosis is not Significantly Linked to COVID-19 Vaccines or Non-COVID Vaccines in a Large Multi-State Health System

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Objective: To assess the association of COVID-19 vaccines and non-COVID-19 vaccines with cerebral venous sinus thrombosis (CVST). *Materials and method:* We retrospectively analyzed a cohort of 771,805 vaccination events across 266,094 patients in the Mayo Clinic Health System between 01/01/2017 and 03/15/2021. The primary outcome was a positive diagnosis of CVST, identified either by the presence of a corresponding ICD code or by an NLP algorithm which detected positive diagnosis of CVST within free-text clinical notes. For each vaccine we calculated the relative risk by dividing the incidence of CVST in the 30 days following vaccination to that in the 30 days preceding vaccination. *Results:* We identified vaccination events for all FDA-approved COVID-19 vaccines including Pfizer-BioNTech (n = 94,818 doses), Moderna (n = 36,350 doses) and Johnson & Johnson - J&J (n = 1,745 doses). We also identified vaccinations events for 10 common FDA-approved non-COVID-19 vaccines (n = 771,805 doses). There was no statistically significant difference in the incidence rate of CVST in 30-days before and after vaccination for any vaccine in this population. We further found the baseline CVST incidence in the study population between 2017 and 2021 to be 45 to 98 per million patient years. *Conclusions:* This real-world evidence-based study finds that CVST is rare and is not significantly associated with COVID-19 vaccination in our patient cohort. Limitations include the rarity of CVST in our dataset, a relatively small number of J&J COVID-19 vaccination events, and the use of a population drawn from recipients of a SARS-CoV-2 PCR test in a single health system.

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Introduction

83 million doses of the Moderna mRNA vaccine, and 6 million doses of the Johnson & Johnson (Janssen) adenovirus vectored vaccine have been administered in the United States.¹ In six patients who received the J&J vaccine (reporting rate 0.87 per million) there have been reports of the development of a rare and dangerous adverse event, cerebral venous sinus thrombosis (CVST) associated with thrombocytopenia, in the weeks following vaccine administration.^{2,3} All six cases occurred among women between the ages of 18 and 48, a high-risk group

for this condition,⁴ and symptoms occurred 6 to 13 days after vaccination.⁵

Although there is no consensus regarding the causality of these associations or their appropriate impact on vaccine use,⁶ this phenotype has now been dubbed vaccine-induced immune thrombotic thrombocytopenia (VITT).⁷ This name derives from the similar laboratory and clinical findings in patients with heparin induced thrombocytopenia (HIT). Notable findings include thrombosis in unusual locations, most notably cerebral venous sinuses, and thrombocytopenia.

Of note, concerns surrounding CVST and VITT primarily involve adenovirus vectored vaccines. Thus far similar concerns have not been raised with regard to the two mRNA vaccines authorized for use in the United States (Pfizer/BioNTech and Moderna). However, there are reports of CVST occurring in individuals after receiving the mRNA vaccines,⁷ and one group found a 4 in 1 million risk of developing CVST following receipt of an mRNA vaccine in their study cohort.⁸ The accumulation of case reports led to a pause of the adenoviral vectored J&J vaccine in the United States, which has led to increased vaccine hesitancy.⁹ In light of this, it is critical to better understand how COVID-19 vaccines affect the risk of developing CVST, and specifically whether any FDA-approved COVID-19 vaccines (mRNA or adenoviral) demonstrably increases the risk of developing CVST and/or VITT. This study investigates these questions by leveraging a large multi-state EHR system to analyze individuals who have received over 130,000 doses of COVID-19 vaccines and over 771,000 doses of non-COVID-19 vaccines.

Materials and methods

Institutional review board (IRB)

This is a retrospective study of individuals who underwent polymerase chain reaction (PCR) testing for suspected SARS-CoV-2 infection at the Mayo Clinic and hospitals affiliated with the Mayo Clinic Health System. This study was reviewed by the Mayo Clinic Institutional Review Board (IRB) and determined to be exempt from the requirement for IRB approval (45 CFR 46.104d, category 4). Subjects were excluded if they did not have a research authorization on file.

Study design, setting and population

This is a retrospective study of individuals who were vaccinated in the Mayo Clinic hospital system between January 1, 2017 and March 15, 2021 and also received at least one SARS-CoV-2 PCR test (Fig. 1). The outcome of interest was cerebral venous sinus thrombosis, identified either by the presence of a corresponding ICD code (I67.6, I63.6, O22.5, G08.X) or by an NLP algorithm that detected a positive diagnosis of CVST of synonyms concepts in their clinical notes (eMethods in Supplement). Clinicians manually reviewed the patients identified as positive for CVST by either ICD code or NLP

algorithm to confirm that the patient's note contained an acute diagnosis of CVST. Subjects were excluded if they did not have a research authorization on file. No subjects were excluded on the basis of demographics, comorbidities, or other clinical characteristics.

Incidence rates

Incidence rates of first-time CVST were calculated as the number of events observed within a given time period divided by the total number of patient-years in the observation period (Fig. 2). For the calculation of background incidence rates from 2017 to present, each of the 30-day windows following the 771,305 vaccine administrations were removed from the total number of patient-years of observation; any CVST events occurring within these windows were not counted towards the background incidence rate and the corresponding patients were removed from the cohort at the time of CVST occurrence. For the calculation of incidence rates within vaccine risk windows, the observation period was defined as the 1–30-day period following vaccine administration. Confidence intervals are $1.96 \times \text{standard error (SE)}$ where $SE = (N/t^2)^{0.5}$; N is the number of CVST events and t is the observation period duration multiplied by the number of patients under observation.

Statistical analysis

We described the characteristics and frequency of cases of CVST stratified by vaccine. For each vaccine, we reported the number of patients newly diagnosed with CVST for the following time periods: +1 to +30 days after the vaccine dose, +1 to +15 days after the vaccine dose, -30 to -1 days before the vaccine dose, and -15 to -1 days before the vaccine dose. We set an at-risk window for CVST post-vaccination to 30 days as all cases reported thus far in the literature and VAERS fell within this window. We defined the relative risk to be post-vaccination incidence in the (+1 to +30 days) divided by the pre-vaccination incidence (-30 to -1 days), and we reported 95% confidence intervals for this metric. In addition, we computed Fisher exact test p-values for the null hypothesis that the relative risk is equal to one. Analyses were conducted in the Python programming language.

Augmented curation of unstructured clinical notes

We used artificial intelligence (AI) driven augmented curation of EHR clinical notes from 266,094 patients between January 1, 2017 and April 15, 2021 from the Mayo Clinic health system to determine CVST diagnoses and other comorbidities. The augmented curation approach has been detailed previously.¹⁰ Briefly, we used previously developed and detailed state-of-the-art BERT-based neural networks to rapidly curate clinical notes that were authored within 6 months of and COVID-19

diagnoses. Specifically, the model extracts sentences containing clinical phenotypes and symptoms and classifies their sentiment into the following categories: Yes (confirmed clinical manifestation or diagnosis), No (ruled out clinical manifestation or diagnosis), Maybe (possibility of clinical manifestation or diagnosis), and Other (alternate context, e.g., family history of disease). The neural networks are pre-trained on 3.17 billion tokens from the biomedical and computer science domains (SciBERT) and subsequently trained using 18,490 sentences and approximately 250 phenotypes with an emphasis on cardiovascular, pulmonary, and metabolic phenotypes. It achieves 93.6% overall accuracy and over 95% precision and recall for both “Yes” and “No” sentiment classification.

Vaccine adverse event reporting system review

We also looked at the data collected by Vaccine Adverse Event Reporting System (VAERS).¹¹ We searched for records of any vaccine that had any of the following adverse events: (10007830) Cavernous Sinus Thrombosis, (10061251) Intracranial Venous Sinus Thrombosis, (10042567) Superior Sagittal Sinus Thrombosis, (10008138) Cerebral Venous Thrombosis, (10083037) Cerebral Venous Sinus Thrombosis, (10044457) Transverse Sinus Thrombosis within 30 days. As of April 17, 2021, VAERS has data up to April 10, 2021.

Results

We determined the background incidence rate of CVST at the Mayo Clinic, defined as the incidence rate of CVST excluding all 30-day time windows following the administration of any non-SARS-CoV-2 vaccines (266,094 unique patients, 771,805 vaccination events). In total, 165 CVST events were identified. The incidence rate ranged from 45 to 98 per million patient years between 2017 and 2021 (Fig. 1A). We then investigated the occurrence of CVST in individuals receiving a COVID-19 vaccine or various non-COVID-19 vaccines. Of the 132,916 total COVID-19 vaccine doses administered, 1,745 were the Janssen vaccine, 36,352 were the Moderna and 94,819 the Pfizer/BioNTech. 771,805 non-COVID-19 vaccine doses were captured in our cohort. We computed annual CVST incidence rates in the non-SARS-CoV-2 vaccine risk window (Fig. 1B) and the incidence rate to-date in the SARS-CoV-2 (Fig. 1C) vaccine risk window. These incidence rates ranged from 0 to 125 per million patient years for non-SARS-CoV-2 vaccines and 292 per million patient years for SARS-CoV-2 vaccines, though the standard errors in these cases were larger than the computed incidence rates. Among the 165 cases of CVST identified since 2017, four patients also had thrombocytopenia (platelets < 150k/ul) within 3 days of CVST diagnosis, for an incidence rate of 2 per million patient years. In three cases, platelets were in the 133k-146k/ul range, and in one case, platelets were in the 74k-84k/ul range. None of these cases occurred in the 30 days following a vaccination of any type.

Among patients receiving any COVID-19 vaccine, there were 10 cases of CVST observed (0.0019%) in the 30 days following vaccine administration, and 10 cases of CVST were observed in the 30 days prior to administration. 3 of the 10 post-vaccination CVST cases were from individuals receiving the Pfizer/BioNTech vaccine, but there were also 3 cases among this same cohort in the 30-day pre-vaccination window, suggesting that these events were likely not caused by the vaccine (RR: 1.0, 95% CI: [0.23, 4.40] (Table 1). To date, no cases of CVST have been documented within 30 days before or after any doses of the Moderna or Janssen vaccines at the Mayo Clinic (Table 1). The relative risk of CVST in the 30 days following any COVID-19 vaccination was not statistically significant (RR: 1.50, 95% CI: [0.28, 7.10], see Table 1).

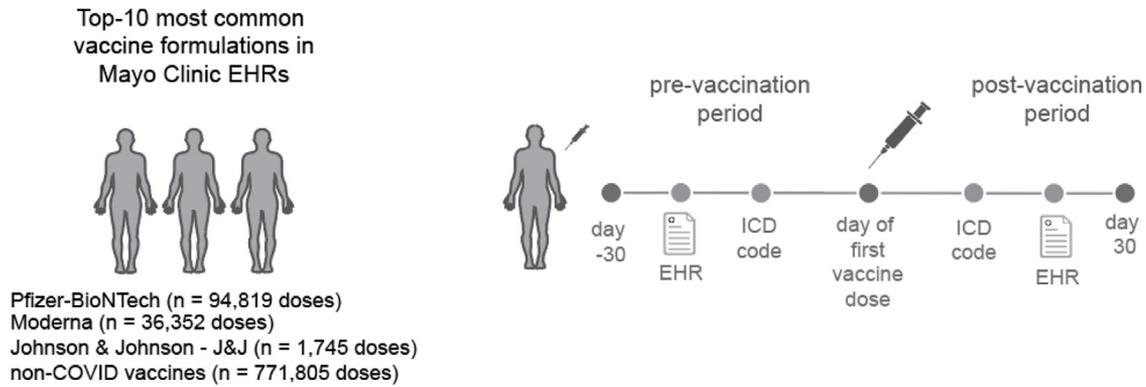
The clinical characteristics of the patients in the study population with CVST and the subset of patients with CVST following COVID-19 vaccination is provided in Table 2. In total, we observed 3 cases of CVST within the 30 days following Pfizer-BioNTech vaccination (2 females, 1 male; Ages (years): [79, 80, 84]), including one individual with a prior history of thrombosis and another individual with recent trauma in the past 30 days. The older ages of these patients and lack of concurrent thrombocytopenia further suggests that these events were distinct from the VITT phenotype which has been reported predominantly in younger females. As compared to all individuals who experienced CVST regardless of vaccination status, patients experiencing CVST after receiving a COVID-19 vaccine generally were older (81.4 +/- 2.8 years old vs. 47.7 +/- 22.3 years old) and had more comorbidities (2.3 +/- 2.1 comorbidities vs. 1.3 +/- 1.6 comorbidities). These differences are unsurprising given that older individuals were prioritized for COVID-19 vaccination.

Discussion

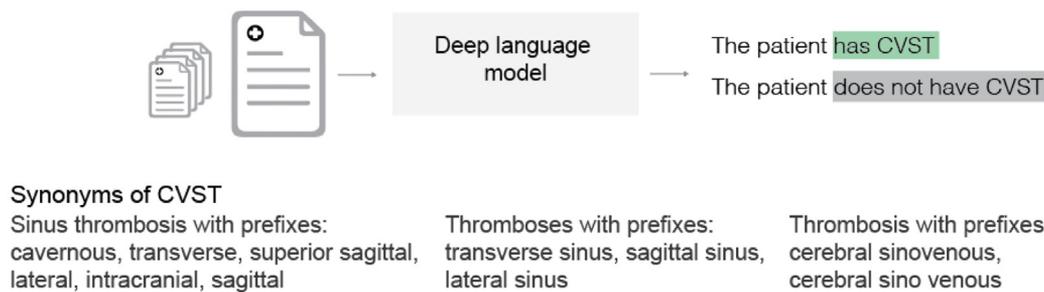
Vaccines to prevent COVID-19 were developed and tested at an unprecedented pace over the past year. They have shown excellent effectiveness both in randomized clinical trials and in the real world setting.¹²⁻¹⁴ While no major safety concerns were identified during the large Phase 3 trials of each authorized vaccine, it is important that their safety is continually assessed throughout the vaccine rollout process. Recent case reports of individuals experiencing CVST with thrombocytopenia shortly after receiving an adenoviral vector COVID-19 vaccine and increased reporting of CVST in VAERS following COVID-19 vaccination as compared to historical rates (Supplementary Table 1) have raised safety concerns, and led to the temporary suspension of some COVID-19 vaccines.

While it is important to consider this reporting in pharmacovigilance decision-making, there is reason to interpret such reports with caution. Spontaneous adverse event reporting is prone to reporting bias and increased event reporting with lay press attention or the introduction of a novel agent.¹⁵⁻¹⁷

a. Examination of incidence of Cerebral venous sinus thrombosis (CVST) in vaccination patients



b. Identify instances of CVST based on context from EHR notes using augmented curation and manual review



c. Comparison of CVST incidence rates in the pre-vaccination and post-vaccination periods

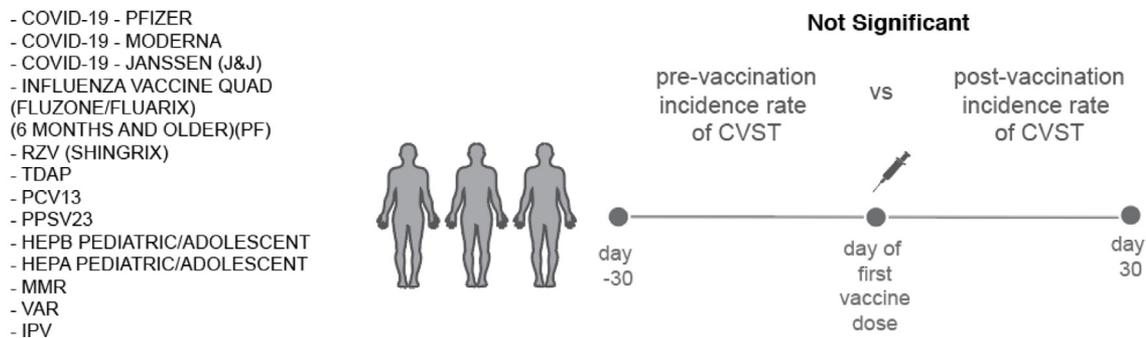


Fig. 1. Overview of the analysis of Cerebral venous sinus thrombosis (CVST) from the EHR database of a multi-state health system. (a) Examination of incidence of Cerebral venous sinus thrombosis (CVST) in vaccination patients. (b) Identify instances of CVST based on context from EHR notes. (c) Comparison of CVST incidence rates in the pre-vaccination and post-vaccination periods.

During this time it is critical to rapidly extract and analyze the content of EHR systems throughout the United States in order to validate or refute whether the risk for this phenotype is in fact increased by one or more authorized vaccines. In this retrospective study of vaccine recipients across a large multi-state healthcare system, we did not detect any significant association between COVID-19 vaccination status and the development of CVST.

Specifically, we found that (1) the risk of CVST was similar in the 30 days prior to COVID-19 vaccination compared to the 30 days after vaccination; (2) the risk of CVST

within 30 days of COVID-19 vaccination was similar to the risk of CVST within 30 days of all analyzed non-COVID vaccinations; and (3) the risk of CVST after COVID-19 vaccination was similar to the baseline risk of CVST across a large cohort of patients in a multi-state healthcare system.

Our analysis demonstrates that to date no FDA-approved vaccine for COVID-19 or otherwise has been associated with a statistically significant increased relative risk of cerebral venous sinus thrombosis in the Mayo Clinic Health System. Given the power of our analysis, it

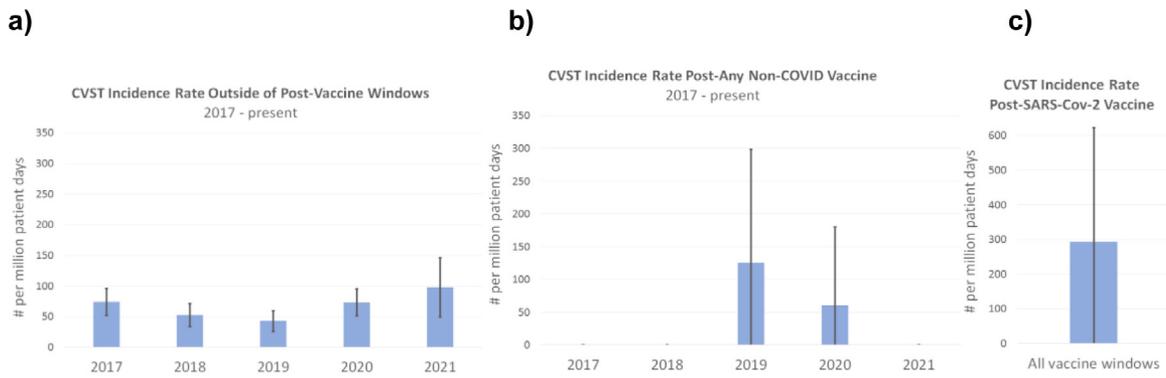


Fig. 2. Incidence rates of cerebral venous sinus thrombosis (CVST) in the study population. Individuals included in this plot are those who received a SARS-CoV-2 polymerase chain reaction (PCR) test at the Mayo Clinic in 2020-21. Incidence of CVST is defined as the first attribution of a diagnosis of CVST to a patient within a physician note, after removal of sentences referring to past occurrences of CVST. A vaccine risk window is defined as the 30 days following administration of a vaccine. **a)** The annual incidence rates of CVST outside of vaccine risk windows (top 10 non-SARS-CoV-2 vaccines and SARS-CoV-2 vaccines). **b)** The annual incidence rates of CVST in the vaccine risk window for the top 10 non-SARS-CoV-2 vaccines administered from January 1, 2017 to April 15, 2021. **c)** The incidence rate of CVST following any SARS-CoV-2 vaccine. Error bars depict standard error.

will be important to confirm these results in higher-powered future studies. The average CVST incidence rate seen in our cohort was 71.7 per million patient years. If this rate was extrapolated across the United States we would expect to see approximately 19 cases of CVST in the 14 days after vaccination amongst the 7 million patients who have received the Johnson & Johnson vaccine by chance alone, while there have been only 6 reported cases to date. This is in line with earlier research demonstrating that the incidence rate of venous thromboembolism was no higher than expected following viral vector vaccine administration¹⁸ and was similar across COVID-19 vaccines.⁸ Of note, our cohort incidence rate was several times the highest prevalence rate of 20.2 per million reported in a recent American cohort.¹⁹ This is likely due to our data originating from tertiary care hospitals and our ability to find CVST diagnoses in free-text as well as recorded ICD-10 codes. Further real-world evidence studies are needed to confirm these findings, but pharmacovigilance regulators should consider such evidence when making decisions regarding the critically important vaccine roll out.

This study has several limitations. First, we analyzed data from a single health system which is demographically distinct from the broader United States population. In addition, the study population was restricted to individuals who have received at least one PCR test for SARS-CoV-2 at the Mayo Clinic, which is different from the overall vaccinated population. Second, as a retrospective study our analyses are inherently limited to only the data which was deemed necessary for collection during the clinical care of each patient. For example, platelet counts are not available for most individuals within 30 days of any vaccination and

quantification of anti-PF4 antibodies are even more sparse. Other clinical covariates not included in the analysis such as oral contraceptives and smoking status may be potential confounding factors. Finally, our cohort contains 1,745 individuals who received the Johnson & Johnson (Janssen) COVID-19 vaccine. Given that VITT has only been reported in 6 of approximately 7 million recipients of this vaccine,²⁰ we are unlikely to detect a signal for it in this cohort.

Despite these limitations, the estimation of the baseline incidence rate for CVST, as well as for CVST with thrombocytopenia, in a cohort of over 600,000 individuals is useful to contextualize the reported frequencies of CVST and VITT in patients receiving all authorized COVID-19 vaccines. Furthermore, while there has been a case study reporting CVST after influenza vaccination,²¹ this is the first study to our knowledge reporting the relative risk of CVST following any of non-COVID-19 vaccines examined. Our findings highlight that CVST is likely an under-reported entity in the VAERS database. Clinicians should be vigilant for and report this event after any vaccination in order to facilitate further research into the nature of vaccine associated thrombosis.

Data availability

After publication, the data will be made available upon reasonable requests to the corresponding author. A proposal with detailed description of study objectives and the statistical analysis plan will be needed for evaluation of the reasonability of requests. Deidentified data will be provided after approval from the corresponding author and the Mayo Clinic.

Table 1. Comparison of cerebral venous sinus thrombosis (CVST) cases recorded pre- and post-vaccination in the Mayo Clinic EHR data. Results are shown for the top-10 most common vaccine formulations in the Mayo Clinic EHR database, along with the three FDA-authorized COVID-19 vaccines (Pfizer/BioNTech, Moderna, and Janssen). Vaccine dose totals are provided for the study time period of January 1, 2017 to March 15, 2021. Neural network models applied to clinical notes were used to determine initial CVST diagnoses. For each vaccine formulation, CVST patient counts are shown for the following time periods: +1 to +30 days after the vaccine dose, -30 to -1 days before the vaccine dose, +1 to +15 days after the vaccine dose, and -1 to -15 days before the vaccine dose. The relative risk is defined as the post-vaccination incidence (+1 to +30 days) divided by the pre-vaccination incidence (-30 to -1 days). In the last column, a p-value for Fisher exact test is shown for the null hypothesis that the relative risk is equal to one. Rows are sorted by total number of vaccine doses. Totals for all vaccines, non-COVID-19 vaccines, and COVID-19 vaccines are shown in the bottom rows in bold.

Vaccine Name	Total Number of Doses	Number of patients with initial diagnoses of CVST				Relative Risk [95% CI]	Fisher Exact Test p-value
		+1 to +30 days post-vaccination	-31 to -1 days pre-vaccination	+1 to +15 days post-vaccination	-15 to -1 days pre-vaccination		
INFLUENZA VACCINE QUAD (FLUZONE/FLUARIX) (6 MONTHS AND OLDER) (PF)	334229	3	4	3	3	0.75 [0.19, 3.14]	1.00
RZV (SHINGRIX)	112062	0	2	0	1	0.00 [0.00, 4.17]	0.50
TDAP	94895	0	2	0	0	0.00 [0.00, 4.17]	0.50
SARS-COV-2 (COVID-19) - PFIZER	94818	3	2	1	2	1.50 [0.28, 7.10]	1.00
PCV13	78672	0	0	0	0	NA	1.00
PPSV23	51746	0	1	0	0	0.00 [0.00, 8.18]	1.00
SARS-COV-2 (COVID-19) - MODERNA	36350	0	0	0	0	NA	1.00
HEPB PEDIATRIC/ADOLESCENT	32265	0	0	0	0	NA	1.00
HEPA PEDIATRIC/ADOLESCENT	27390	0	0	0	0	NA	1.00
MMR	19560	0	0	0	0	NA	1.00
VAR	16368	0	0	0	0	NA	1.00
IPV	4618	0	0	0	0	NA	1.00
SARS-COV-2 (COVID-19) - JANSSEN (J&J)	1745	0	0	0	0	NA	1.00
All vaccines	904718	10	10	6	6	1.00 [0.43, 2.35]	1.00
Non-COVID-19 vaccines	771805	7	8	5	4	0.88 [0.33, 2.36]	1.00
COVID-19 vaccines	132913	3	2	1	2	1.50 [0.28, 7.10]	1.00

Table 2. Clinical characteristics of CVST patients (overall and following COVID-19 vaccination). Charlson comorbidities are determined by ICD codes. Other comorbidities including autoimmune disorders, heart disease, hemoglobinopathy, hypercoagulability syndrome, inflammatory bowel disease (IBD), thrombosis, and trauma are determined from the clinical notes using deep neural network models. The phenotype for trauma is determined using clinical notes from the past 30 days, and for all other phenotypes, clinical notes or ICD codes from the past 10 years are considered (relative to the CVST diagnosis date).

Clinical Characteristics	All CVST Patients (n = 105)	CVST following COVID-19 vaccination (n = 3)
Age in years		
Mean (std dev)	52.4 (22.3)	81.4 (2.8)
< 18	7 (6.7%)	0 (0.0%)
19-35	17 (16.2%)	0 (0.0%)
36-49	20 (19.0%)	0 (0.0%)
50-64	26 (24.8%)	0 (0.0%)
>= 65	35 (33.3%)	3 (100.0%)
Sex		
Female	64 (61.0%)	2 (66.7%)
Male	41 (39.0%)	1 (33.3%)
Race		
Asian	4 (3.8%)	0 (0.0%)
Black/African American	4 (3.8%)	0 (0.0%)
White/Caucasian	92 (87.6%)	3 (100.0%)
Other	2 (2.9%)	0 (0.0%)
Unknown	1 (1.9%)	0 (0.0%)
Ethnicity		
Hispanic or Latino	5 (4.8%)	0 (0.0%)
Not Hispanic or Latino	99 (94.3%)	3 (100.0%)
Unknown	1 (1.0%)	0 (0.0%)
BMI (kg/m ²)		
Mean (std dev)	28.7 (7.3)	29.0 (9.3)
Data availability	51 (48.6%)	3 (100.0%)
Comorbidity		
Autoimmune disorders	7 (6.7%)	0 (0.0%)
Cancer (localized)	6 (5.7%)	1 (33.3%)
Cancer (metastatic)	0 (0.0%)	0 (0.0%)
Congestive heart failure	2 (1.9%)	0 (0.0%)
Dementia	0 (0.0%)	0 (0.0%)
Diabetes	8 (7.6%)	0 (0.0%)
Diabetes (with complications)	1 (1.0%)	0 (0.0%)
Heart disease	22 (21.0%)	2 (66.7%)
Hemoglobinopathy	0 (0.0%)	0 (0.0%)
HIV/AIDS	0 (0.0%)	0 (0.0%)
Hypercoagulability syndrome	10 (9.5%)	0 (0.0%)
IBD	5 (4.8%)	0 (0.0%)
IBD	6 (5.7%)	1 (33.3%)
Liver disease (mild-to-moderate)	1 (1.0%)	0 (0.0%)
Liver disease (severe)	3 (2.9%)	0 (0.0%)
Myocardial infarction	0 (0.0%)	0 (0.0%)
Myocardial infarction	2 (1.9%)	0 (0.0%)

(Continued)

Table 2 (Continued)

Clinical Characteristics	All CVST Patients (n = 105)	CVST following COVID-19 vaccination (n = 3)
Paralysis	7 (6.7%)	0 (0.0%)
Peptic ulcer disease	10 (9.5%)	1 (33.3%)
Peripheral vascular disease	6 (5.7%)	0 (0.0%)
Pulmonary disease	2 (1.9%)	0 (0.0%)
Pulmonary disease	6 (5.7%)	0 (0.0%)
Renal disease	29 (27.6%)	1 (33.3%)
Rheumatic disease	5 (4.8%)	1 (33.3%)
Stroke		
Thrombosis		
Trauma		
Number of comorbidities		
Mean (std dev)	1.3 (1.6)	2.3 (2.1)

Author contributions

VS, CP, SA and PL conceived the study. All authors wrote sections of the manuscript and reviewed the findings. The authors from nference contributed methods, analysis, and software tools. The authors from Mayo Clinic reviewed the study design, clinical findings, and the manuscript's health policy implications. All authors revised the manuscript based on feedback received.

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Declaration of Competing Interest

JCO receives personal fees from Elsevier and Bates College, and receives small grants from nference, Inc, outside the submitted work. ADB is a consultant for Abbvie, is on scientific advisory boards for nference and Zentaris, and is founder and President of Splissen therapeutics. nference collaborates with Janssen and other bio-pharmaceutical companies on data science initiatives unrelated to this study. These collaborations had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. JRH, JCO, GJG, AWW, AV, MDS, and ADB are employees of the Mayo Clinic. This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and is being conducted in compliance with Mayo Clinic Conflict of Interest policies.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2021.105923.

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